NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Ramucirumab for treating advanced gastric cancer or gastro-oesophageal junction adenocarcinoma after chemotherapy [ID741]

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - **Eli Lilly and Company**

   No comment' response received from the Department of Health and the Royal College of Nursing

3. **Comments on the Appraisal Consultation Document received through the NICE website**

4. **Impact of Evidence Review Group changes provided post ACD**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SingleTechnology Appraisal

Ramucirumab for treating advanced gastric cancer or gastro–oesophageal junction adenocarcinoma previously treated with chemotherapy

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment [sic]	Response
Lilly	Variation in second-line treatment practice across England Across regions in England there is unwarranted variation and inequity in the provision of second-line treatment for advanced GC/GOJ. The lack of a licensed second-line treatment for advanced GC/GOJ might have contributed to the apparent lack/reduction in opportunities and need for clinicians to meet, discuss and debate the use of second-line treatments for this rare, aggressive and difficult-to-treat cancer. The Appraisal Committee did not consider inequality of access to cancer treatments an issue that a technology appraisal can address. Lilly disagrees with this statement, as one of the main reasons NICE was originally set up in 1999 was "to reduce variation in the availability and quality of NHS treatments and care"[2]. NICE guidance on a new medicine might not be the only factor that will reduce the inequality patients experience with cancer treatments, but having a NICE recommended treatment option is a first step towards achieving that goal.	The Committee considered this comment at the second Appraisal Committee meeting. However, as discussed in section 4.20 of the FAD, it remained of the view that this was an issue of geographical variation and it was not aware that the potential inequality in access applied to any protected groups covered by the equality legislation. It also considered that any NICE recommendation would be applied consistently across England, thereby reducing variation in practice. It concluded that there was no unfairness or unlawful discrimination, and as a result there were no equality issues, and it did not need to alter its recommendations in any way.
Lilly	Network meta-analysis (NMA) The Evidence Review Group (ERG) criticised the inclusion of an Asian-specific trial (Hironaka, 2013) and a small German trial (Thuss-Patience, 2011) in the NMA Lilly	See section 4.6 of the FAD: "The Committee noted comments from the company during consultation that the early termination of the trial was

Consultee	Comment [sic]	Response
	submitted. Lilly believes that the weaknesses of the NMA has been overestimated (rational provided below), and that the results should be considered sufficiently plausible to permit its use. *Thuss-Patience (2011)* The Thuss-Patience trial is criticised for being small and stopping recruitment early. However, it would not have been valid to exclude the trial only on the grounds of small population numbers. A small trial will be limited only in terms of the certainty attached to the results and this will already be incorporated in the NMA results. If the trial was stopped for positive efficacy (or futility), the trial results could have been biased. However the early termination of the trial was related to difficulties in recruitment, rather than efficacy, so the trial results should still be systemically unbiased.	related to difficulties in recruitment, rather than efficacy, so the trial results should still be unbiased. However, the Committee, noting that the trial was based on a sample of only 40 randomised patients, considered the point estimates for the treatment effect to be associated with considerable uncertainty."
Lilly	*Hironaka (2013)* Differences in treatment practices in Asia have led to better survival outcomes for patients with GC/GOJ compared to those in the UK. These differences will only widen further if the UK, for whatever reason, fails to adopt innovative treatment practices that have been shown to benefit patients. The Appraisal Committee discussion of the Hironaka study in the ACD focused on the fact that the study population were entirely Japanese (who have a national screening programme to identify the disease in the earlier stages), and that clinical experts at the Appraisal Committee meeting suggested that patients in the Hironaka study had much longer survival gains than is typically seen in UK clinical practice. However, Lilly does not believe that there is any clinical rationale that the <u>relative</u> treatment effect of paclitaxel versus irinotecan in patients with metastatic or recurrent gastric adenocarcinoma is different in patients in Asia compared to Europe. That is, there is no clear biological rationale that if the Hironaka trial was repeated in Europe, the true underlying hazard ratio would not be the same. As the relative treatment effect rather than the absolute treatment effect drives the results from the NMA, the results should be considered plausible.	See section 4.6 of the FAD: "The Committee noted comments from the company during consultation that there was no clear biological rationale for why the hazard ratio from the Hironaka et al. study (which relied on the relative rather than absolute treatment effect of paclitaxel compared with irinotecan) would be different in a western population. However, the Committee noted that no evidence had been presented to confirm that this would be the case, and so it was still of the opinion that there was significant uncertainty about using the results of this trial in the network

<table>
<tr><th>Consultee</th><th>Comment [sic]</th><th>Response</th></tr>
<tr><td></td><td></td><td>meta-analysis.”</td></tr>
<tr><td>Lilly</td><td>
Impact of direct evidence on ICER
A comparison of the overall survival (OS) and progression-free survival (PFS) results from the NMA, the indirect treatment comparison and the results from the RAINBOW trial show that the outputs are reasonably similar and therefore the direct evidence is comparable to the indirect evidence.

Table 1: Comparison of overall survival results from RAINBOW trial, indirect treatment comparison and NMA. Comparisons of treatment A vs. treatment B, HR (95% CrI).
<table>
<tr><th rowspan="2">Treatment A</th><th colspan="3">Treatment B – paclitaxel</th></tr>
<tr><th>RAINBOW trial</th><th>Indirect treatment comparison</th><th>Network meta-analysis</th></tr>
<tr><td>Ramucirumab plus paclitaxel</td><td>0.807 (0.678, 0.962)</td><td>0.81 (0.68, 0.96)</td><td>0.81 (0.68, 0.96)</td></tr>
</table>
NMA, Network Meta-Analysis; CrI, credible interval; HR, hazard ratio

Table 2: Comparison of progression-free survival results from RAINBOW trial, indirect treatment comparison and NMA. Comparisons of treatment A vs. treatment B, HR (95% CrI).
<table>
<tr><th rowspan="2">Treatment A</th><th colspan="3">Treatment B – paclitaxel</th></tr>
<tr><th>RAINBOW trial</th><th>Indirect treatment comparison</th><th>Network meta-analysis</th></tr>
<tr><td>Ramucirumab plus paclitaxel</td><td>0.635 (0.536, 0.752)</td><td>0.64 (0.54, 0.75)</td><td>0.64 (0.54, 0.75)</td></tr>
</table>
NMA, Network Meta-Analysis; CrI, credible interval; HR, hazard ratio

When using the direct trial evidence in the model rather than the evidence from the NMA the ICER increased by 8 percent. However, the way that the results of this
</td><td>Comments noted. The FAD has been amended to reflect the comments that the ACD did not clearly reflect the impact that using the trial data had on the combination therapy model outcomes. See section 3.46. In addition, section 3.38 of the FAD has been moved so it is clearer that the results presented in table 1 use the company’s base case assumptions.</td></tr>
</table>

Consultee	Comment [sic]	Response
	analysis is presented in section 3.46 of the ACD does not clearly reflect the limited impact this particular change in the combination therapy model has on the outcome, and can be perceived to be the main driver for the change in the ICER from the base-case of £273,657 to £408,200.	
Lilly	<u>Comparators</u> The Appraisal Committee's consideration of the cost-effectiveness and end-of-life status evidence for ramucirumab plus paclitaxel has predominantly been presented in comparison to paclitaxel in this ACD. However, it was clear from the discussion at the Appraisal Committee meeting and the evidence presented by Lilly that BSC and docetaxel are important clinical comparators due to their widespread use as second-line treatment options. Comments from the clinical experts at the Appraisal Committee meeting supported this: in a recent scoping exercise for a clinical trial one of the clinical experts reported that the vast majority of contacted centres used docetaxel and only a few used paclitaxel; the other clinical expert commented that a number of centres across the country do not actively treat second-line patients at all. Even though the clinical experts at the Appraisal Committee stated that they currently use weekly paclitaxel, they were clear that it was appropriate and necessary to compare ramucirumab combination therapy to BSC and docetaxel as part of this appraisal. In addition, NICE included BSC, docetaxel monotherapy, irinotecan monotherapy, FOLFIRI, and paclitaxel monotherapy as comparators for this appraisal in the final scope. Of these the Appraisal Committee concluded that only irinotecan monotherapy and FOLFERI are not relevant comparators because they are not in established use. It can therefore be assumed that BSC, docetaxel and paclitaxel were considered relevant comparators for ramucirumab combination therapy. Lilly does not agree with the Appraisal Committee's justification for its selection of the most plausible ICER as this decision was made mainly as a result of the Committee's conclusion that "the results of the network meta-analysis should not be used in preference to data from direct head-to-head comparisons"[1]. In our view the weaknesses of the NMA have been overestimated and we consider the results	The Committee do not make a distinction between paclitaxel and docetaxel regarding which is a more appropriate comparator. Section 4.3 of the FAD states: "The Committee concluded that for people for whom ramucirumab combination therapy is appropriate, paclitaxel and docetaxel were **<u>both</u>** relevant comparators and are in established use in clinical practice in England." Regarding the comments that best supportive care is an appropriate comparator for combination therapy. Section 4.3 of the FAD states: "The Committee understood that people who are considered fit for ramucirumab in combination with paclitaxel must by definition be able to tolerate paclitaxel monotherapy. Given this rationale in conjunction with the comments from clinical experts, the Committee was not

Consultee	Comment [sic]	Response
	sufficiently plausible to permit their use. Lilly believes that the cost-effectiveness case for ramucirumab combination therapy will be more fairly presented by providing multiple or a range of possible ICERs (which represents all relevant comparators), with recognition that the most plausible ICER for this appraisal will lie within that range. Finally, the Appraisal Committee concluded that ramucirumab combination therapy fulfilled two of the three end-of-line criteria. The committee decided that the extension-to-life criterion for ramucirumab combination therapy was not met based on the comparison with paclitaxel. The decision not to consider the overall survival gains for the other two relevant comparators (BSC and docetaxel) was due to the NMA not being considered plausible or robust but there is no evidence to support this criticism. Given the step-change improvement in survival over BSC (6.03 months) and docetaxel (4.13 months), it is clear that ramucirumab combination therapy meets the end-of-life criteria.	persuaded that best supportive care was an appropriate comparator for the ramucirumab plus paclitaxel population. Please see above comments regarding the Committee's views on the NMA. In addition, please note section 4.6 of the FAD: "The Committee concluded that for the basis of decision-making, the results of the network meta-analysis would not be used in preference to the RAINBOW trial data comparing ramucirumab plus paclitaxel with paclitaxel plus placebo."
Lilly	<u>Factual inaccuracies and inconsistencies</u> *Incorrect calculation of average cost of a course of treatment with ramucirumab* Under section 2.4 of the ACD, the average cost of a course of treatment with ramucirumab was presented as £42,000 per person (excluding VAT). This cost has been incorrectly calculated. The treatment cost per patient for monotherapy using NICE's calculations should be £21,000 as the drug cost per cycle is £3000. • Drug cost per dose: 8mg/kg*63.33kg = 506.64mg which requires 1 x 50ml vial and 1 x 10ml vial (£2500 + £500 = £3000). • In the monotherapy trial, a cycle consisted of 14 days (not 28 days as is the case in the combination therapy trial). Therefore, patients only received one dose per 14 day cycle. • Patient received an average of 7 cycles (cycle of 14 day duration) – rounded	Comments noted. The FAD has been amended to reflect the calculations presented by Lilly. Please see section 2.4 of the FAD.

Consultee	Comment [sic]	Response
	up from a mean of 6.94 cycles. The treatment cost per patient for combination therapy using NICE's calculations should be £36,000, as the drug cost per cycle is £6000. • Drug cost per dose: 8mg/kg*63.33 = 506.64mg which requires 1 x 50ml vial and 1 x 10ml vial (£2500 + £500 = £3000). • In the combination therapy trial, a cycle consisted of 28 days. Therefore, patients received 2 doses per cycle. • Patients received an average of 6 cycles – rounded from a mean of 6.17 cycles. It is not appropriate to round this up to 7 rather than down to 6.	
Lilly	*Inconsistent reference to the percentage of patients receiving second-line treatments* The Appraisal Committee's statements regarding the percentage of people who go on to having second-line treatment after progressing on chemotherapy was not presented consistently and, according to Lilly, did not clearly represent the statements made by the clinical experts. Lilly believes that it was clear from the discussion at the Appraisal Committee meeting that the percentage of patients who go on to receive active second-line treatment is 30% of all first-line patients who received treatment, and not 30% of all GC/GOJ patients as presented in section 4.16.	Comment noted. The Committee considered the estimated population size in the second Appraisal Committee meeting. Section 4.16 of the FAD has been amended to reflect the Committee's views.
	Impact of COUGAR II on UK clinical practice There seems to be a misunderstanding regarding the impact of COUGAR II on UK clinical practice as the ACD states that the use of paclitaxel would be expected to increase after the positive results for paclitaxel from COUGAR II. However, COUGAR II included docetaxel three-weekly, not paclitaxel. Lilly is concerned that this error might have influenced the Appraisal Committee's assessment of the comparators which led to paclitaxel being considered the most plausible comparator. However, the results of COUGAR II are more likely to lead to an	NICE acknowledge that the ACD contained an error that suggested paclitaxel was a treatment in COUGAR II. The Committee was made aware of this error in the second Appraisal Committee meeting. Section 3.37 of the FAD has been amended to reflect the Committee's views in light of this error being corrected:

Consultee	Comment [sic]	Response
	increase in real-world use of docetaxel, which further supports Lilly's view that docetaxel is a more relevant comparator than paclitaxel.	"The ERG also commented that the company's survey of real-world treatment patterns was based on data from June to July 2013, and that since then favourable results for docetaxel from the COUGAR II study have been published, which may have resulted in increased real-world use of taxanes in general (paclitaxel as well as docetaxel).

Lilly

Table with minor corrections/clarifications

	Section number	Current statement in ACD	Proposed statement / clarification
1	3.2	"time to progression on first-line therapy"	time to progression **from the start of** ~~**on**~~ first-line therapy
2	3.4	"A high proportion of people in RAINBOW were male (71%) and most were white (61% white, 35% Asian, 4% black)."	A high proportion of people in RAINBOW were male (71%) and most were white (61% white, 35% Asian, 4% black **and other**).
3	3.4	"Previous trastuzumab therapy was had by 20 people in the ramucirumab plus paclitaxel arm compared with 11 people in the placebo plus paclitaxel arm."	Previous trastuzumab therapy was had by 20 people in the ramucirumab plus paclitaxel arm compared with ~~**11**~~ **19** people in the placebo plus paclitaxel arm.
4	3.9	"The company presented the outcomes for region 1 showing that in this subgroup there was a 2.66-month greater median overall survival (p=0.0050), and 1.41-month greater progression-free survival (p<0.0001) for ramucirumab plus paclitaxel compared with placebo plus paclitaxel. The median survival times for both treatment arms in the intention-to-treat population of RAINBOW were longer compared with those for region 1, which the company	The company presented the outcomes for region 1 showing that in this subgroup there was a 2.66-month greater median overall survival (p=0.0050), and 1.41-month greater **median** progression-free survival (p<0.0001) for ramucirumab plus paclitaxel compared with placebo plus paclitaxel. The median survival times for both treatment arms in the intention-to-treat population of RAINBOW were longer compared with those for region 1, which the company

Consultee		Comment [sic]	Response
		attributed to the higher rates of third-line chemotherapy use among Asian people after stopping treatment with ramucirumab."	attributed to the higher rates of third-**and fourth-**line chemotherapy use among Asian people after stopping treatment with ramucirumab.
	3.10	"The study, which started in 2009, involved adults with advanced gastric cancer or gastro–oesophageal junction adenocarcinoma who had disease progression on or within 4 months of treatment with first-line, platinum-containing or fluoropyrimidine-containing, chemotherapy."	The study, which started in 2009, involved adults with advanced gastric cancer or gastro–oesophageal junction adenocarcinoma who had disease progression on or within 4 months **after the last dose** of treatment with first-line, platinum-containing or fluoropyrimidine-containing, chemotherapy **or on or within 6 months after last dose of adjuvant therapy**.
6	3.11	"The trial randomised 355 adults in a 2:1 ratio to have ramucirumab 8 mg/kg (n=236) or placebo (n=115) intravenously once every 2 weeks (in contrast to RAINBOW, in which treatment was given every 28 days)."	The trial randomised 355 adults in a 2:1 ratio to have ramucirumab 8 mg/kg (n=~~**236**~~ **238**) or placebo (n=~~**115**~~ **117**) intravenously once every 2 weeks ~~**(in contrast to RAINBOW, in which treatment was given every 28 days)**~~. *Comment: The treatment cycle in the RAINBOW trial was 28 days to accommodate the paclitaxel dosing schedule. However, ramucirumab was given on days 1 and 15 of that 28 day cycle (so in effect given once every 2 weeks).*
7	3.12	"People in the trial had metastatic disease or locally recurrent, unresectable disease, a life expectancy of 12 weeks or less and an ECOG performance status score of 0 or 1"	People in the trial had metastatic disease or locally recurrent, unresectable disease, a life expectancy of 12 weeks or ~~**less**~~ **more** and an ECOG performance status score of 0 or 1
8	3.13	"Median overall survival was 5.2 months for ramucirumab plus best supportive care and 3.8 months for placebo plus best supportive care (1.4-month improvement in survival; HR 0.78; 95% CI 0.60 to 1.0; p=0.047). Median progression-free survival was 2.1 months for ramucirumab plus best supportive care and 1.3 months for placebo plus best supportive care (0.8-month improvement in progression-free survival; HR 0.48; 95% CI 0.38 to 0.62; p=0.0001."	Median overall survival was 5.2 months for ramucirumab plus best supportive care and 3.8 months for placebo plus best supportive care (1.4-month improvement in **median** survival; HR 0.78; 95% CI 0.60 to 1.0; p=0.047). Median progression-free survival was 2.1 months for ramucirumab plus best supportive care and 1.3 months for placebo plus best supportive care (0.8-month improvement in **median** progression-free survival; HR 0.48; 95% CI 0.38 to 0.62; ~~**p=0.0001**~~ **p<0.0001**.
9	3.14	"At 6 weeks, the proportion of patients with improved or stable quality of life was higher for the ramucirumab	At 6 weeks, the proportion of patients with improved or stable quality of life was higher for the ramucirumab

Consultee		Comment [sic]	Response
		arm (34.1%) than the placebo arm (13.7%); but the difference was not statistically significant (p=0.23)."	arm (34.1%) than the placebo arm (13.7%); but the difference was not statistically significant (p=0.23) **between those with QoL data**.
10	3.15	"Overall safety results for the REGARD trial showed similar numbers of people in each group had at least 1 serious adverse event; 45% in the ramucirumab group compared with 44% in the placebo group. There was a greater proportion of people who stopped treatment in the ramucirumab group (11.3%) compared with the placebo group (6.1%)."	Overall safety results for the REGARD trial showed similar ~~numbers~~ **percentages** of people in each group had at least 1 serious adverse event; 45% in the ramucirumab group compared with 44% in the placebo group. There was a greater proportion of people who stopped treatment in the ramucirumab group (~~11.3~~ **10.5**%) compared with the placebo group (~~6.1~~ **6.0**%).
11	3.17	"Results from the network meta-analysis suggested that ramucirumab plus paclitaxel was associated with a statistically significantly improved overall survival compared with best supportive care (HR 0.34; 95% CI 0.17 to 0.71), paclitaxel (HR 0.81; 95% CI 0.68 to 0.96), and irinotecan (HR 0.71; 95% CI 0.52 to 0.99), and with a numerically (but not statistically significant) improved overall survival compared with docetaxel (HR 0.51; 95% CI 0.23 to 1.13) and FOLFIRI (HR 0.86; 95% CI 0.45 to 1.65)."	Results from the ~~network meta-analysis~~ **indirect comparison** suggested that ramucirumab plus paclitaxel was associated with a statistically significantly improved overall survival compared with best supportive care (HR 0.34; 95% CI 0.17 to 0.71), paclitaxel (HR 0.81; 95% CI 0.68 to 0.96), and irinotecan (HR ~~0.71~~ **0.72**; 95% CI 0.52 to 0.99), and with a numerically (but not statistically significant) improved overall survival compared with docetaxel (HR 0.51; 95% CI 0.23 to 1.13) and FOLFIRI (HR 0.86; 95% CI 0.45 to 1.65).
12	3.37	"The ERG also commented that the company's survey of real-world treatment patterns was based on data from June to July 2013, and that since then, favourable results for paclitaxel from the COUGAR II study have been published, which may have resulted in increased real-world use of paclitaxel."	The ERG also commented that the company's survey of real-world treatment patterns was based on data from June to July 2013, and that since then, favourable results for ~~paclitaxel~~ **docetaxel** from the COUGAR II study have been published, which may have resulted in increased real-world use of ~~paclitaxel~~ **docetaxel**.
13	4.11	"The Committee was mindful of its previous conclusions that paclitaxel and docetaxel are appropriate comparators for ramucirumab	The Committee was mindful of its previous conclusions that **BSC,** paclitaxel and docetaxel are appropriate comparators for ramucirumab

Consultee	Comment [sic]	Response
	combination therapy…"	combination therapy… *Comment: The Appraisal Committee did not exclude BSC as a relevant comparator for ramucirumab combination therapy (only irinotecan and FOLFERI were excluded).*

Response from NICE on table with minor corrections/clarifications:

Comments in the table copied above were each considered and corrections have been made in the FAD where appropriate. The proposed statements / clarifications NICE does not agree with are:

- Section 3.37 of the ACD (see section 3.37 of the FAD): "The ERG also commented that the company's survey of real world treatment patterns was based on data from June to July 2013, and that since then favourable results for docetaxel from the COUGAR II study have been published, which may have resulted in increased real world use of taxanes in general (paclitaxel as well as docetaxel)."
- Section 4.11 of the ACD (see section 4.11 of the FAD): "The Committee was mindful of its previous conclusions that paclitaxel and docetaxel are both appropriate comparators for ramucirumab combination therapy"

Department of Health	No comments	
Royal College of Nursing	No comments	

Comments received from clinical experts and patient experts

Nominating organisation	Comment [sic]	Response
	No comments received from clinical experts and patient experts	

Comments received from commentators

Commentator	Comment [sic]	Response
	No comments received from commentators	

Comments received from members of the public

Role*	Section	Comment [sic]	Response
NHS Professional		This group of patients currently have limited options for treatment. I treat any patients with metastatic gastric (or GOJ) cancers that relapse after first line treatment (which is usually EOX) on an individual basis but would tend to offer palliative chemo with docetaxel. This is a toxic treatment so patients inevitably have to be of good performance status, WHO 0 or 1.	
NHS Professional		For this group of cancer, which carries a poor prognosis, the therapeutic options for palliation is rather limited. Also it is associated with considerable toxicities. Targetted agents are not available for UGI cancers and hence Ramucirumumab would give an much needed treatment option. I would whole heartedly welcome this agent to become available.	

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Eli Lilly and Company Limited

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6 October 2015

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M1 4BT

RE: Ramucirumab for treating advanced gastric cancer or gastro-oesophageal junction adenocarcinoma after chemotherapy [ID741]: Eli Lilly and Company Limited response to the Appraisal Consultation Document (ACD)

Dear Meindert

Thank you for the opportunity to respond to the Appraisal Consultation Document (ACD) on ramucirumab for treating patients with advanced gastric cancer (GC) or gastro–oesophageal junction adenocarcinoma (GOJ) previously treated with chemotherapy.

Lilly is pleased that the Appraisal Committee has recognised that ramucirumab is the first biologic agent to show efficacy in people whose disease had progressed after chemotherapy, and that it provides an active treatment option for people for whom cytotoxic chemotherapy is not appropriate in this area of high unmet medical need. It is disappointing that the innovative nature of ramucirumab was only considered in relation to the health-related benefits captured by the QALYs in the model, with no acknowledgement of the wider and dynamic impact ramucirumab could have on clinical practice, patients and future medical advances. Prior to ramucirumab, anti-angiogenic molecules that have targeted different receptors within the VEGF pathway have failed to show a significant impact on GC/GOJ overall survival outcomes, which means there has been no proven licenced treatments for second-line, advanced GC/GOJ. Ramucirumab has demonstrated efficacy in the second-line setting in two phase III trials, providing an alternative to cytotoxic chemotherapy. It is Lilly's hope that the planned integrated appraisal process currently under development (between NHS England and NICE) will include reformed approaches to the way new cancer medicines will be considered and ensure that these wider benefits of innovation are taken into account in the future.

According to section 4.3 in the ACD, the Appraisal Committee concluded that "for people for whom ramucirumab combination therapy is appropriate, paclitaxel and docetaxel are both relevant comparators and are in established use in clinical practice in England"[1]. In addition, best supportive care (BSC) was not excluded as a relevant comparator, which is in line with Lilly's position that BSC is an important comparator in this appraisal. The Incremental Cost Effectiveness Ratio (ICER) of ramucirumab combination therapy compared to paclitaxel has however been selected as the most plausible ICER by the Appraisal Committee for the ramucirumab combination therapy model. This decision implies that the Appraisal Committee considers paclitaxel the most relevant comparator for ramucirumab

combination therapy. Lilly does not agree with the Appraisal Committee's approach and justification for selecting this ICER, and believe the decision is unreasonable in the light of the evidence submitted to NICE which shows that BSC and docetaxel are more widely used in the NHS than paclitaxel. We acknowledge that there is some uncertainty in determining the most plausible ICER, and therefore suggest that in this instance multiple or a range of plausible ICERs (which represents all the relevant comparators in this appraisal) is a more reasonable and fair approach. In addition, Lilly believes that the overall survival gains of all relevant comparators should be considered when determining if the end-of-life criteria has been met.

Our response to this ACD focuses mainly on (1) the variation in use of second-line GC/GOJ treatments in clinical practice, (2) the Network Meta-Analysis (NMA) discussion and conclusions, and (3) the comparators selected for this appraisal. In addition, we have identified a number of factual inaccuracies and inconsistencies we would like to address (4).

1. <u>Variation in second-line treatment practice across England</u>

Across regions in England there is unwarranted variation and inequity in the provision of second-line treatment for advanced GC/GOJ. The lack of a licensed second-line treatment for advanced GC/GOJ might have contributed to the apparent lack/reduction in opportunities and need for clinicians to meet, discuss and debate the use of second-line treatments for this rare, aggressive and difficult-to-treat cancer.

The Appraisal Committee did not consider inequality of access to cancer treatments an issue that a technology appraisal can address. Lilly disagrees with this statement, as one of the main reasons NICE was originally set up in 1999 was "to reduce variation in the availability and quality of NHS treatments and care"[2]. NICE guidance on a new medicine might not be the only factor that will reduce the inequality patients experience with cancer treatments, but having a NICE recommended treatment option is a first step towards achieving that goal.

2. <u>Network meta-analysis (NMA)</u>

The Evidence Review Group (ERG) criticised the inclusion of an Asian-specific trial (Hironaka, 2013) and a small German trial (Thuss-Patience, 2011) in the NMA Lilly submitted. Lilly believes that the weaknesses of the NMA has been overestimated (rational provided below), and that the results should be considered sufficiently plausible to permit its use.

Thuss-Patience (2011)
The Thuss-Patience trial is criticised for being small and stopping recruitment early. However, it would not have been valid to exclude the trial only on the grounds of small population numbers. A small trial will be limited only in terms of the certainty attached to the results and this will already be incorporated in the NMA results. If the trial was stopped for positive efficacy (or futility), the trial results could have been biased. However the early termination of the trial was related to difficulties in recruitment, rather than efficacy, so the trial results should still be systemically unbiased.

Hironaka (2013)

Differences in treatment practices in Asia have led to better survival outcomes for patients with GC/GOJ compared to those in the UK. These differences will only widen further if the UK, for whatever reason, fails to adopt innovative treatment practices that have been shown to benefit patients. The Appraisal Committee discussion of the Hironaka study in the ACD focused on the fact that the study population were entirely Japanese (who have a national screening programme to identify the disease in the earlier stages), and that clinical experts at the Appraisal Committee meeting suggested that patients in the Hironaka study had much longer survival gains than is typically seen in UK clinical practice. However, Lilly does not believe that there is any clinical rationale that the relative treatment effect of paclitaxel versus irinotecan in patients with metastatic or recurrent gastric adenocarcinoma is different in patients in Asia compared to Europe. That is, there is no clear biological rationale that if the Hironaka trial was repeated in Europe, the true underlying hazard ratio would not be the same. As the relative treatment effect rather than the absolute treatment effect drives the results from the NMA, the results should be considered plausible.

Impact of direct evidence on ICER

A comparison of the overall survival (OS) and progression-free survival (PFS) results from the NMA, the indirect treatment comparison and the results from the RAINBOW trial show that the outputs are reasonably similar and therefore the direct evidence is comparable to the indirect evidence.

Table 1: Comparison of overall survival results from RAINBOW trial, indirect treatment comparison and NMA. Comparisons of treatment A vs. treatment B, HR (95% CrI).

Treatment A	Treatment B – paclitaxel		
	RAINBOW trial	Indirect treatment comparison	Network meta-analysis
Ramucirumab plus paclitaxel	***0.807 (0.678, 0.962)***	***0.81 (0.68, 0.96)***	***0.81 (0.68, 0.96)***

NMA, Network Meta-Analysis; Crl, credible interval; HR, hazard ratio

Table 2: Comparison of progression-free survival results from RAINBOW trial, indirect treatment comparison and NMA. Comparisons of treatment A vs. treatment B, HR (95% CrI).

Treatment A	Treatment B – paclitaxel		
	RAINBOW trial	Indirect treatment comparison	Network meta-analysis
Ramucirumab plus paclitaxel	***0.635 (0.536, 0.752)***	***0.64 (0.54, 0.75)***	***0.64 (0.54, 0.75)***

NMA, Network Meta-Analysis; Crl, credible interval; HR, hazard ratio

When using the direct trial evidence in the model rather than the evidence from the NMA the ICER increased by 8 percent. However, the way that the results of this analysis is presented in section 3.46 of the ACD does not clearly reflect the limited impact this particular change in the combination therapy model has on the outcome, and can be perceived to be the main driver for the change in the ICER from the base-case of £273,657 to £408,200.

3. Comparators

The Appraisal Committee's consideration of the cost-effectiveness and end-of-life status evidence for ramucirumab plus paclitaxel has predominantly been presented in comparison to paclitaxel in this ACD. However, it was clear from the discussion at the Appraisal Committee meeting and the evidence presented by Lilly that BSC and docetaxel are important clinical comparators due to their widespread use as second-line treatment options. Comments from the clinical experts at the Appraisal Committee

meeting supported this: in a recent scoping exercise for a clinical trial one of the clinical experts reported that the vast majority of contacted centres used docetaxel and only a few used paclitaxel; the other clinical expert commented that a number of centres across the country do not actively treat second-line patients at all. Even though the clinical experts at the Appraisal Committee stated that they currently use weekly paclitaxel, they were clear that it was appropriate and necessary to compare ramucirumab combination therapy to BSC and docetaxel as part of this appraisal. In addition, NICE included BSC, docetaxel monotherapy, irinotecan monotherapy, FOLFIRI, and paclitaxel monotherapy as comparators for this appraisal in the final scope. Of these the Appraisal Committee concluded that only irinotecan monotherapy and FOLFERI are not relevant comparators because they are not in established use. It can therefore be assumed that BSC, docetaxel and paclitaxel were considered relevant comparators for ramucirumab combination therapy.

Lilly does not agree with the Appraisal Committee's justification for its selection of the most plausible ICER as this decision was made mainly as a result of the Committee's conclusion that "the results of the network meta-analysis should not be used in preference to data from direct head-to-head comparisons"[1]. In our view the weaknesses of the NMA have been overestimated and we consider the results sufficiently plausible to permit their use.

Lilly believes that the cost-effectiveness case for ramucirumab combination therapy will be more fairly presented by providing multiple or a range of possible ICERs (which represents all relevant comparators), with recognition that the most plausible ICER for this appraisal will lie within that range.

Finally, the Appraisal Committee concluded that ramucirumab combination therapy fulfilled two of the three end-of-line criteria. The committee decided that the extension-to-life criterion for ramucirumab combination therapy was not met based on the comparison with paclitaxel. The decision not to consider the overall survival gains for the other two relevant comparators (BSC and docetaxel) was due to the NMA not being considered plausible or robust but there is no evidence to support this criticism. Given the step-change improvement in survival over BSC (6.03 months) and docetaxel (4.13 months), it is clear that ramucirumab combination therapy meets the end-of-life criteria.

4. <u>Factual inaccuracies and inconsistencies</u>

Incorrect calculation of average cost of a course of treatment with ramucirumab

Under section 2.4 of the ACD, the average cost of a course of treatment with ramucirumab was presented as £42,000 per person (excluding VAT). This cost has been incorrectly calculated.

The treatment cost per patient for <u>monotherapy</u> using NICE's calculations should be <u>£21,000</u> as the drug cost per cycle is £3000.

- Drug cost per dose: 8mg/kg*63.33kg = 506.64mg which requires 1 x 50ml vial and 1 x 10ml vial (£2500 + £500 = £3000).
- In the monotherapy trial, a cycle consisted of 14 days (not 28 days as is the case in the combination therapy trial). Therefore, patients only received one dose per 14 day cycle.
- Patient received an average of 7 cycles (cycle of 14 day duration) – rounded up from a mean of 6.94 cycles.

The treatment cost per patient for combination therapy using NICE's calculations should be £36,000, as the drug cost per cycle is £6000.

- Drug cost per dose: 8mg/kg*63.33 = 506.64mg which requires 1 x 50ml vial and 1 x 10ml vial (£2500 + £500 = £3000).
- In the combination therapy trial, a cycle consisted of 28 days. Therefore, patients received 2 doses per cycle.
- Patients received an average of 6 cycles – rounded from a mean of 6.17 cycles. It is not appropriate to round this up to 7 rather than down to 6.

Inconsistent reference to the percentage of patients receiving second-line treatments

The Appraisal Committee's statements regarding the percentage of people who go on to having second-line treatment after progressing on chemotherapy was not presented consistently and, according to Lilly, did not clearly represent the statements made by the clinical experts. Lilly believes that it was clear from the discussion at the Appraisal Committee meeting that the percentage of patients who go on to receive active second-line treatment is 30% of all first-line patients who received treatment, and not 30% of all GC/GOJ patients as presented in section 4.16.

Impact of COUGAR II on UK clinical practice

There seems to be a misunderstanding regarding the impact of COUGAR II on UK clinical practice as the ACD states that the use of paclitaxel would be expected to increase after the positive results for paclitaxel from COUGAR II. However, COUGAR II included docetaxel three-weekly, not paclitaxel.

Lilly is concerned that this error might have influenced the Appraisal Committee's assessment of the comparators which led to paclitaxel being considered the most plausible comparator. However, the results of COUGAR II are more likely to lead to an increase in real-world use of docetaxel, which further supports Lilly's view that docetaxel is a more relevant comparator than paclitaxel.

Table with minor corrections/clarifications

Table 3 (which can be found at end of this document) contains a list of minor corrections and clarifications to the ACD.

We hope the information presented in this response will help the Appraisal Committee ensure that the evidence for ramucirumab combination therapy is considered and presented in a fair and consistent manner by (1) including multiple or a range of plausible ICERs which represents all the relevant comparators in this appraisal and (2) by considering the overall survival gains of all relevant comparators when determining if the end-of-life criteria has been met.

Yours sincerely,

[redacted]

Table 3: Minor corrections and clarifications to ACD

	Section number	Current statement in ACD	Proposed statement / clarification
1	3.2	"time to progression on first-line therapy"	time to progression **from the start of** ~~on~~ first-line therapy
2	3.4	"A high proportion of people in RAINBOW were male (71%) and most were white (61% white, 35% Asian, 4% black)."	A high proportion of people in RAINBOW were male (71%) and most were white (61% white, 35% Asian, 4% black **and other**).
3	3.4	"Previous trastuzumab therapy was had by 20 people in the ramucirumab plus paclitaxel arm compared with 11 people in the placebo plus paclitaxel arm."	Previous trastuzumab therapy was had by 20 people in the ramucirumab plus paclitaxel arm compared with ~~11~~ **19** people in the placebo plus paclitaxel arm.
4	3.9	"The company presented the outcomes for region 1 showing that in this subgroup there was a 2.66-month greater median overall survival (p=0.0050), and 1.41-month greater progression-free survival (p<0.0001) for ramucirumab plus paclitaxel compared with placebo plus paclitaxel. The median survival times for both treatment arms in the intention-to-treat population of RAINBOW were longer compared with those for region 1, which the company attributed to the higher rates of third-line chemotherapy use among Asian people after stopping treatment with ramucirumab."	The company presented the outcomes for region 1 showing that in this subgroup there was a 2.66-month greater median overall survival (p=0.0050), and 1.41-month greater **median** progression-free survival (p<0.0001) for ramucirumab plus paclitaxel compared with placebo plus paclitaxel. The median survival times for both treatment arms in the intention-to-treat population of RAINBOW were longer compared with those for region 1, which the company attributed to the higher rates of third-**and fourth-**line chemotherapy use among Asian people after stopping treatment with ramucirumab.
5	3.10	"The study, which started in 2009, involved adults with advanced gastric cancer or gastro–oesophageal junction adenocarcinoma who had disease progression on or within 4 months of treatment with first-line, platinum-containing or fluoropyrimidine-containing, chemotherapy."	The study, which started in 2009, involved adults with advanced gastric cancer or gastro–oesophageal junction adenocarcinoma who had disease progression on or within 4 months **after the last dose** of treatment with first-line, platinum-containing or fluoropyrimidine-containing, chemotherapy **or on or within 6 months after last dose of adjuvant therapy**.
6	3.11	"The trial randomised 355 adults in a 2:1 ratio to have ramucirumab 8 mg/kg (n=236) or placebo (n=115) intravenously once every 2 weeks (in contrast to RAINBOW, in which treatment was given every 28 days)."	The trial randomised 355 adults in a 2:1 ratio to have ramucirumab 8 mg/kg (n=~~236~~ **238**) or placebo (n=~~115~~ **117**) intravenously once every 2 weeks ~~**(in contrast to RAINBOW, in which treatment was given every 28 days)**~~. *Comment: The treatment cycle in the RAINBOW trial was 28 days to accommodate the paclitaxel dosing schedule. However, ramucirumab was given on days 1 and 15 of that 28 day cycle (so in effect given once every 2 weeks).*
7	3.12	"People in the trial had metastatic disease or locally recurrent, unresectable disease, a life expectancy of 12 weeks or less and an ECOG performance status score of 0 or 1"	People in the trial had metastatic disease or locally recurrent, unresectable disease, a life expectancy of 12 weeks or ~~less~~ **more** and an ECOG performance status score of 0 or 1

8	3.13	"Median overall survival was 5.2 months for ramucirumab plus best supportive care and 3.8 months for placebo plus best supportive care (1.4-month improvement in survival; HR 0.78; 95% CI 0.60 to 1.0; p=0.047). Median progression-free survival was 2.1 months for ramucirumab plus best supportive care and 1.3 months for placebo plus best supportive care (0.8-month improvement in progression-free survival; HR 0.48; 95% CI 0.38 to 0.62; p=0.0001."	Median overall survival was 5.2 months for ramucirumab plus best supportive care and 3.8 months for placebo plus best supportive care (1.4-month improvement in **median** survival; HR 0.78; 95% CI 0.60 to 1.0; p=0.047). Median progression-free survival was 2.1 months for ramucirumab plus best supportive care and 1.3 months for placebo plus best supportive care (0.8-month improvement in **median** progression-free survival; HR 0.48; 95% CI 0.38 to 0.62; ~~**p=0.0001**~~ **p<0.0001**.
9	3.14	"At 6 weeks, the proportion of patients with improved or stable quality of life was higher for the ramucirumab arm (34.1%) than the placebo arm (13.7%); but the difference was not statistically significant (p=0.23)."	At 6 weeks, the proportion of patients with improved or stable quality of life was higher for the ramucirumab arm (34.1%) than the placebo arm (13.7%); but the difference was not statistically significant (p=0.23) **between those with QoL data**.
10	3.15	"Overall safety results for the REGARD trial showed similar numbers of people in each group had at least 1 serious adverse event; 45% in the ramucirumab group compared with 44% in the placebo group. There was a greater proportion of people who stopped treatment in the ramucirumab group (11.3%) compared with the placebo group (6.1%)."	Overall safety results for the REGARD trial showed similar ~~**numbers**~~ **percentages** of people in each group had at least 1 serious adverse event; 45% in the ramucirumab group compared with 44% in the placebo group. There was a greater proportion of people who stopped treatment in the ramucirumab group (~~**11.3**~~ **10.5**%) compared with the placebo group (~~**6.1**~~ **6.0**%).
11	3.17	"Results from the network meta-analysis suggested that ramucirumab plus paclitaxel was associated with a statistically significantly improved overall survival compared with best supportive care (HR 0.34; 95% CI 0.17 to 0.71), paclitaxel (HR 0.81; 95% CI 0.68 to 0.96), and irinotecan (HR 0.71; 95% CI 0.52 to 0.99), and with a numerically (but not statistically significant) improved overall survival compared with docetaxel (HR 0.51; 95% CI 0.23 to 1.13) and FOLFIRI (HR 0.86; 95% CI 0.45 to 1.65)."	Results from the ~~**network meta-analysis**~~ **indirect comparison** suggested that ramucirumab plus paclitaxel was associated with a statistically significantly improved overall survival compared with best supportive care (HR 0.34; 95% CI 0.17 to 0.71), paclitaxel (HR 0.81; 95% CI 0.68 to 0.96), and irinotecan (HR ~~**0.71**~~ **0.72**; 95% CI 0.52 to 0.99), and with a numerically (but not statistically significant) improved overall survival compared with docetaxel (HR 0.51; 95% CI 0.23 to 1.13) and FOLFIRI (HR 0.86; 95% CI 0.45 to 1.65).
12	3.37	"The ERG also commented that the company's survey of real-world treatment patterns was based on data from June to July 2013, and that since then, favourable results for paclitaxel from the COUGAR II study have been published, which may have resulted in increased real-world use of paclitaxel."	The ERG also commented that the company's survey of real-world treatment patterns was based on data from June to July 2013, and that since then, favourable results for ~~**paclitaxel**~~ **docetaxel** from the COUGAR II study have been published, which may have resulted in increased real-world use of ~~**paclitaxel**~~ **docetaxel**.
13	4.11	"The Committee was mindful of its previous conclusions that paclitaxel and docetaxel are appropriate comparators for ramucirumab combination therapy…"	The Committee was mindful of its previous conclusions that **BSC,** paclitaxel and docetaxel are appropriate comparators for ramucirumab combination therapy… *Comment: The Appraisal Committee did not exclude BSC as a relevant comparator for ramucirumab combination therapy (only irinotecan and FOLFERI were excluded).*

References

1. NICE. Ramucirumab for treating advanced gastric cancer or gastro–oesophageal junction adenocarcinoma previously treated with chemotherapy. *Appraisal Consultation Document*. London: NICE; September 2015. www.nice.org.uk
2. NICE. 2015. *Who we are* [ONLINE]. Available at: http://www.nice.org.uk/about/who-we-are [Accessed 06 October 2015]

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	NHS Professional
Other role	consultant clinical oncologist
Organisation	
Location	England
Conflict	None
Notes	
Comments on individual sections of the ACD: This group of patients currently have limited options for treatment. I treat any patients with metastatic gastric (or GOJ) cancers that relapse after first line treatment (which is usually EOX) on an individual basis but would tend to offer palliative chemo with docetaxel. This is a toxic treatment so patients inevitably have to be of good performance status, WHO 0 or 1**.**	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3 (The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Name	[redacted]
Role	NHS Professional
Other role	[redacted]
Organisation	Mid Essex Hospitals, NHS, Chelmsford
Location	England
Conflict	None
Notes	
Comments on individual sections of the ACD: For this group of cancer, which carries a poor prognosis, the therapeutic options for palliation is rather limited. Also it is associated with considerable toxicities. Targetted agents are not available for UGI cancers and hence Ramucirumumab would give an much needed treatment option. I would whole heartedly welcome this agent to become available.	
Section 1 (Appraisal Committee's preliminary recommendations)	
Section 2 (The technology)	
Section 3	

(The manufacturer's submission)	
Section 4 (Consideration of the evidence)	
Section 5 (Implementation)	
Section 6 (Related NICE guidance)	
Section 7 (Proposed date of review of guidance)	

Additional information ERG in response to the company's response to the ACD

In this document the impact of the ERG changes to the company base case is explained for both the comparison of RAM+PAC vs DOC and for RAM+PAC vs PAC.
The first table is reproduced from the ERG report. Here we see that the largest changes in the ICER are observed when removing the double counting of hospitalisation for adverse events and when basing weight or body surface on the region 1 population of the clinical study.
Note that all changes result from changes in the costs per treatment, the number of QALYs does not change.
Regarding the impact of basing weight or body surface on the region 1 population, the impact on the DOC costs are minimal, but a clear increase in RAM+PAC costs can be seen. This is due to the fact that weight (RAM dosage) differs more between the whole population and the region 1 population than the body surface area (PAC and DOC dosage).

Cohort	BSA Mean	Weight Mean
All patients	1.71	63.33
Region 1	1.78	68.15

Table 6.2 of ERG report: Revised base case cost-effectiveness analysis, incorporating corrections and amendments identified by the ERG for combination therapy RAM+PAC vs DOC; cumulative results

	DOC		RAM + PAC		Incremental		
	Cost	QALY	Cost	QALY	Cost	QALY	ICER
Company Base case with confirmed errors corrected	£18,849	0.39	£53,003	0.62	£34,153	0.24	£145,302
Corrected docetaxel treatment cost coding error	£18,824	0.39	£53,003	0.62	£34,179	0.24	£145,412
Double counting hospitalisation when AEs corrected	£10,980	0.39	£46,945	0.62	£35,965	0.24	£153,008
Hosp. Rate based on treatment and region	£10,518	0.39	£47,060	0.62	£36,542	0.24	£155,466
BSA/weight based on region 1	£10,523	0.39	£50,050	0.62	£39,527	0.24	£168,164
ERG revised base case	£10,523	0.39	£50,050	0.62	£39,527	0.24	£168,164

In the second table, where RAM + PAC is compared to PAC, we observe that now removing the double counting of hospitalisations for adverse events is clearly the most influential change. This is related to the different adverse event profiles that DOC and PAC have. Here again we see that using only region 1 patients to estimate drug costs only impacts the costs of RAM+PAC substantially. However, here the impact on the ICER is larger than when DOC is the comparator. This is explained by the smaller QALY gain for RAM+PAC versus PAC (0.1 rather than 0.24) and the fact that dividing a cost amount by a smaller QALY gain leads to a relatively much larger increase in the ICER.
In the final row of the RAM+PAC vs PAC table, we see that using the IPD data to model the PAC arm rather than the HR found in the NMA leads to a decrease in the QALY gain thus increasing the ICER to £392,108.

Table 6.2A: Revised base case cost-effectiveness analysis, incorporating corrections and amendments identified by the ERG for combination therapy RAM+PAC vs PAC; cumulative results

	PAC		**RAM + PAC**		**Incremental**		
	Cost	**QALY**	**Cost**	**QALY**	**Cost**	**QALY**	**ICER**
Company Base case with confirmed errors corrected	£26,213	0.52	£53,003	0.62	£26,790	0.1	£273,657
Corrected docetaxel treatment cost coding error	£26,213	0.52	£53,003	0.62	£26,790	0.1	£273,657
Double counting hospitalisation when AEs corrected	£15,454	0.52	£46,945	0.62	£31,491	0.1	£321,679
Hosp. Rate based on treatment and region	£14,820	0.52	£47,060	0.62	£32,240	0.1	£329,337
BSA/weight based on region 1	£14,828	0.52	£50,050	0.62	£35,222	0.1	£359,794
ERG revised base case	£14,828	0.52	£50,050	0.62	£35,222	0.1	£359,794
IPD analysis PAC	£14,938	0.53	£50,050	0.62	£35,112	0.09	£392,108